Nonlinear Additive Isoboles: Importance in Assessing Synergism in Drug Combination Studies

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When two agonist compounds that produce overtly similar effects are administered together the combination's effect may be additive, sub-additive or super-additive. The distinction among these outcomes has obvious clinical (and drug development) importance, but the outcome can also provide important clues on the mechanism of the individual and combination administration. If the individual actions are independent, that is, mediated through different receptors, the detection of synergism indicates an interaction that occurs between their receptor-mediated signals. The distinction between additive and synergistic interactions is often made with the use of an isobole graph. This is a plot, in Cartesian coordinates, that contains the loci of points (dose pairs: (a,b)) that produce a specified effect equal to that of drug A acting alone (in dose A) or drug B acting alone (in dose B). The isobole is determined from the potencies of the individual compounds and is therefore indicative of simple additivity. It is used as a reference curve for comparing the location of the experimentally determined dose pair. If the latter is "on" the isobole the interaction is additive, but if it falls significantly off the isobole there is either synergism or antagonism. Synergism is revealed by a point that is *below* the isobole curve which means that the specified effect was reached with lesser quantities of the constituents. In contrast, an experimental point that lies *above* the isobole is indicative of antagonism. Noisy data can cloud the determination of "above" and "below" and thus requires statistical testing of the kind described by Tallarida (2000). Application of the isobole method is increasing, and the increase is especially notable in experiments with analgesic combinations. In virtually all of these studies the additive isobole is constructed as a straight line segment that connects doses A and B on the intercepts. This construction assumes that the individual compounds have a constant potency ratio [$R= A/B$] and, thus, a dose b of drug B adds an equivalent of drug A that is given by Rb so that the total, $a+b = a + Rb$, is equivalent to A; thus $a + Rb = A$, or $a/A + b/B =1$, a straight line graph. While its use is widespread in isobolographic analysis, the additive isobole may not be a straight line. The consequences of a departure from linearity can be most important in distinguishing between synergistic and simply additive interactions, even in erroneously concluding synergism that is not real. The nonlinearity arises when the individual drugs do not have a constant relative potency (R) but, instead, a value of R that changes over the effect range of effects. This would apply to non-parallel regressions of effect on log (dose) as well as to cases in which the two agents achieve different maximum effects, such as a combination containing a full and a partial agonist. Hence, this graphical-computational approach, so frequently used to detect synergistic interactions, can have a broad impact on combination data interpretation and the associated biomedical discovery process that follow from it.

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Reference

Tallarida, R.J.(2000). *Drug Synergism and Dose-Effect Data Analysis.* Chapman Hall, Boca Raton.